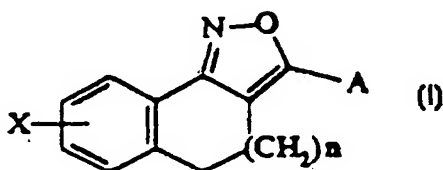


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(54) Title: 4,5-DIHYDRONAPHTH[1,2-C]ISOXAZOLES AND DERIVATIVES THEREOF HAVING CNS ACTIVITY			
(57) Abstract  4,5-Dihydronaphth[1,2-c]isoxazole derivatives of general formula (I), where A, X and n are defined herein are disclosed. Such compounds are useful as serotonin 5-HT <sub>3</sub> antagonists. These compounds are useful for the treatment of anxiety, psychiatric disorders, nausea, vomiting and drug dependency.			
			 <div style="text-align: right;">(I)</div>

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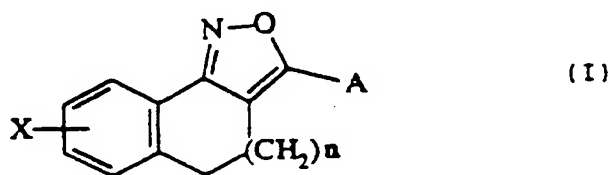
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# 4,5-DIHYDRONAPHTH[1,2-C]ISOXAZOLES AND DERIVATIVES THEREOF HAVING CNS ACTIVITY

The present invention is directed to certain novel compounds and their use as pharmaceutical agents having unique central nervous system activity.

5 This invention relates to 4,5-dihydronaphth[1,2-c]isoxazoles and derivatives thereof, and their use as serotonin 5-HT<sub>1</sub> antagonists, which may be useful for the treatment of anxiety, psychiatric disorders, schizophrenia, nausea, vomiting and the control of drug dependency, of general formula (I):

10

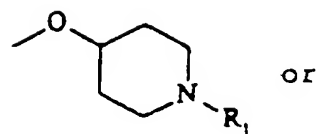
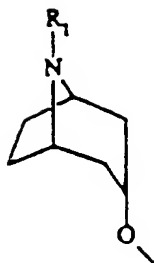
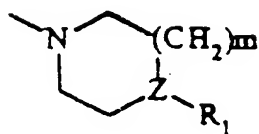


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wherein A is hydrogen, hydroxy,

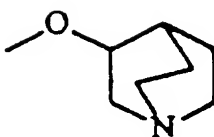
20

5



or

10



wherein

15

$R_1$  is hydrogen, an alkyl group of 1 to 6 carbons, optionally substituted with hydroxy, alkoxy or amino substitution; aryl or heteroaryl, optionally substituted with halogen, hydroxy or alkoxy; or benzyl optionally substituted with halogen, hydroxy or alkoxy;

20

- $n$  is an integer of 1 or 2;
- $Z$  is nitrogen, CH or C(OH);
- $m$  is an integer of 1 to 3; and
- $X$  is hydrogen, hydroxy or alkoxy;

25

or a pharmaceutically acceptable additional salt thereof, or where applicable, a geometric or optical isomer or racemic mixture thereof.

5           The present invention also relates to a process for preparing these compounds, pharmaceutically acceptable addition salts thereof, as well as the pharmaceutical acceptable compositions thereof, and a method of using the compounds as serotonin 5-HT<sub>1</sub> antagonists.

10

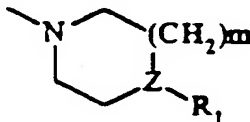
Throughout the specification and appended claims, a given chemical formula or name shall encompass all stereo and optical isomers where such isomers exist. Additionally, a given chemical formula or name shall encompass the pharmaceutically acceptable additional salts thereof.

15

In a preferred embodiment of the invention are compounds of formula (I) wherein

20

A is



wherein

25

$R_1$  is hydrogen, an alkyl group of 1 to 6 carbons,  
optionally substituted with hydroxy, alkoxy or amino  
substitution; aryl or heteroaryl, optionally substituted with  
halogen, hydroxy or alkoxy; or benzyl optionally substituted  
5 with halogen, hydroxy or alkoxy;

$n$  is an integer of 1 or 2;

$Z$  is nitrogen;

10

$m$  is an integer of 1 to 3; and

$X$  is hydrogen, hydroxy or alkoxy.

15

More preferred, are compounds of formula (I) wherein

$R_1$  is hydrogen, or an alkyl group of 1 to 3 carbons;

20

$n$  is 1;

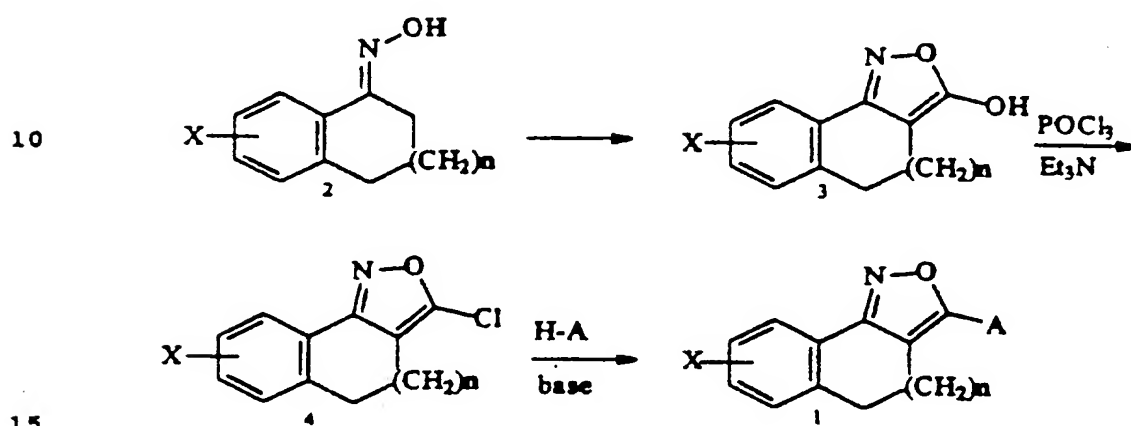
$Z$  is nitrogen;

$m$  is 1 or 2; and

25

X is hydrogen.

The novel compounds of the present invention and the intermediates thereto may be prepared by the reaction sequence illustrated hereinbelow. The substituents Z, m, n and X are generally as defined above unless otherwise indicated.



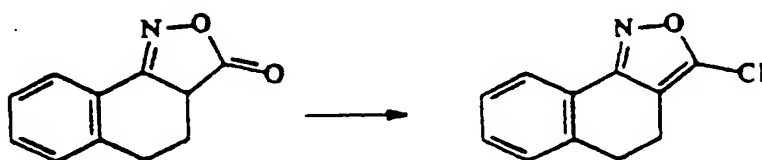
According to the preparation scheme, hydroxyisoxazoles 3 are prepared from oximes 2 in a solvent such as tetrahydrofuran (THF) at a temperature of from about 25°C to about reflux temperature of the solvent for a period of from about 0.25 to about 4 hours according to the methods of Griffiths and Olofson (Jerome S. Griffiths, et al., J. Chem. Soc. C, 974 (1971) and G.N. Barber and R.A. Olofson, J. Org. Chem. 43, 3015 (1978)). The hydroxyisoxazoles 3 are converted to chloroisoxazoles 4 via

treatment with phosphorous oxychloride in the presence of a suitable base, such as triethylamine, at a temperature of from about 100° to about 200°C for a period of from about 0.25 to about 4 hours in a manner similar to that utilized by Adembri et al. (G. Adembri and P. Tedeschi, *Bull. Sci. Fac. Chim. Ind. Bologna* 23, 203 (1965)). Intermediates 4 are treated with an appropriate nucleophile H-A (wherein A is defined hereinbefore) at a temperature of from about 100° to about 200° C with or without added base in an appropriate solvent, such as N-methylpyrrolidinone, to provide the novel compounds 1 of the invention.

These compounds may be prepared by the following representative examples. The examples are exemplary and should not be construed as limiting the invention disclosed herein.

EXAMPLE 1

3-Chloro-4,5-dihydronaphth[1,2-c]isoxazole



To a stirred mixture of 4,5-dihydronaphth[1,2-c]isoxazol-3-one (3aH)-one (7.25g, 38.77mmol) in phosphorus oxychloride (10.84ml, 116.3mmol), triethylamine (5.40ml, 38.77mmol) was added



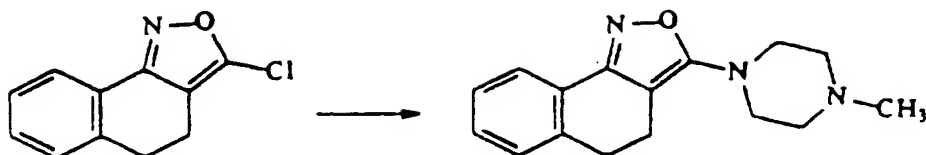
dropwise. After completion of addition, the mixture was heated to reflux while stirring. After 2 hours, no starting material remained as shown by TLC [silica, ethylacetate (EtOAc)]. The mixture was cooled to room temperature, poured into 300 ml of ice water, and extracted with  $\text{CH}_2\text{Cl}_2$ . The organic extracts were combined, dried over  $\text{MgSO}_4$ , and concentrated in vacuo. The resultant solid was filtered through silica using  $\text{CH}_2\text{Cl}_2$  eluent to provide 6.2g of crude product. This crude product was recrystallized from a minimum of heptane to provide a product as needles, mp of 57-59°C, homogeneous by thin layer chromatography (TLC) [silica,  $\text{CH}_2\text{Cl}_2$ ,  $R_f=0.80$ ]. The Infrared (IR) ( $\text{CHCl}_3$ ), nuclear magnetic resonance (NMR) ( $\text{CDCl}_3$ ), and Mass Spectrum ( $M^+=205$ , EI, 70eV) were consistent with the structure. The yield was 5.417g (26.4mmol, 68.16%).

## Elemental Analysis

	Calculated	Found
C	64.25	64.02
H	3.92	3.86
Cl	17.24	
N	6.81	6.77
O	7.78	

EXAMPLE 2

3-(4-Methyl-1-piperazinyl)-4,5-dihydronaphth[1,2-c]isoxazole



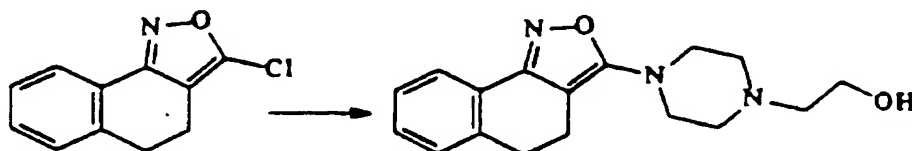
5        A stirred mixture of 3-chloro-4,5-dihydronaphth(1,2-c)isoxazole (2.65g, 12.93mmol), N-methyl piperazine (30ml, 270.4mmol) and  $K_2CO_3$  (3.57g, 25.87mmol) under  $N_2$  was lowered into an oil bath preheated to 150°C. The mixture was heated while stirring under  $N_2$  for 2 hours. At that time, TLC [ $CH_2Cl_2$ ] showed  
10        no remaining starting material. The mixture was removed from the heating bath and allowed to cool to room temperature. It was then partitioned between heptane/ $H_2O$ . The heptane phase was washed with water, dried over  $MgSO_4$ , filtered and concentrated in vacuo to yield a solid. This crude product was  
15        recrystallized from heptane/ether ( $Et_2O$ ) to provide the product as needles, mp of 92-94°C, homogeneous by TLC [silica, 1:1  $CH_3OH:EtOAc$ ,  $R_f=0.39$ ]. The IR ( $CHCl_3$ ), NMR ( $CDCl_3$ ) and Mass Spectrum ( $M^+=269$ , EI, 70eV) were consistent with the structure. The yield was 1.2555g (4.67mmol, 36.09%).

## Elemental Analysis

	Calculated	Found
C	71.35	71.34
H	7.11	6.98
N	15.60	15.78
O	5.94	

## EXAMPLE 3

3-(4-(2-Hydroxyethyl)-1-piperazinyl)-4,5-dihydronaphth[1,2-  
c]isoxazole



A stirred mixture of 3-chloro-4,5-dihydronaphth[1,2-  
c]isoxazole (3.0g, 14.63mmol), 1-(2-hydroxyethyl)-piperazine  
(17.95ml, 146.3mmol) and  $K_2O_3$  (4.1g, 29.3mmol) in 18ml of N-  
methypyrrolidinone under  $N_2$  was lowered into an oil bath  
preheated to 150°C. The mixture was heated while stirring under  
 $N_2$  for 1 hour. At that time, TLC ( $CH_2Cl_2$ ) showed no remaining  
starting material. The mixture was removed from the heating  
bath, allowed to cool to room temperature, and diluted with  $H_2O$ .  
Upon the addition of heptane, a solid precipitated. The solid  
was collected, washed with heptane and  $H_2O$ , and dried in vacuo

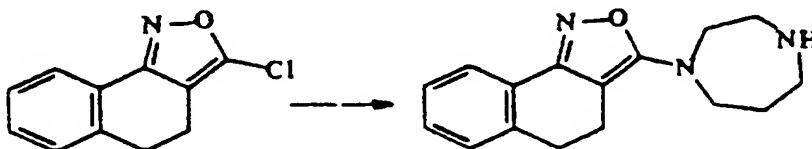
(0.1mm) at 85°C overnight to provide pure product, mp of 137-138°C, homogeneous by TLC [silica, 1:1 CH<sub>3</sub>OH:EtOAc, R<sub>f</sub>=0.67]. The IR (CHCl<sub>3</sub>), NMR (CDCl<sub>3</sub>) and Mass Spectrum (M<sup>+</sup>=299, EI, 70eV) were consistent with the structure. The yield was 2.603g (8.70mmol, 59.47%).

## Elemental Analysis

	Calculated	Found
C	68.21	68.12
H	7.07	7.01
N	14.04	14.14
O	10.69	

## EXAMPLE 4

3-(1-Homopiperazinyl)-4,5-dihydronaphth[1,2-c]isoxazole



A stirred mixture of 3-chloro-4,5-dihydronaphth[1,2-c]isoxazole (3.0g, 14.63 mmol) homopiperazine (14.66g, 146.3 mmol) and K<sub>2</sub>CO<sub>3</sub> (4.04g, 29.3mmol) in 16ml of N-methylpyrrolidinone under N<sub>2</sub> was lowered into an oil bath preheated to 150°C. The mixture was heated while stirring under N<sub>2</sub> for 45 minutes. At that time, TLC (CH<sub>2</sub>Cl<sub>2</sub>) showed no remaining

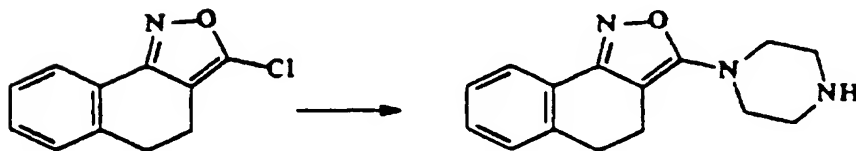
starting material. The mixture was removed from the heating bath, allowed to cool to room temperature, diluted with H<sub>2</sub>O and extracted with Et<sub>2</sub>O. The Et<sub>2</sub>O phase was dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. The crude solid obtained was recrystallized from heptane/Et<sub>2</sub>O and dried in vacuo (0.1mm) at 85°C overnight to provide pure product, mp of 79-81°C, homogeneous by TLC [silica, 1:1 CH<sub>3</sub>OH:EtOAc, R<sub>f</sub>=0.17]. The IR (CHCl<sub>3</sub>), NMR (CDCl<sub>3</sub>) and Mass Spectrum (M<sup>+</sup>=269, EI, 70eV) were consistent with the structure. The yield was 1.969g (7.32mmol, 50.03%).

## Elemental Analysis

	Calculated	Found
C	71.35	71.45
H	7.11	7.29
N	15.60	15.56
O	5.94	

EXAMPLE 5

3-(1-Piperazinyl)-4,5-dihydronaphth[1,2-c]isoxazole



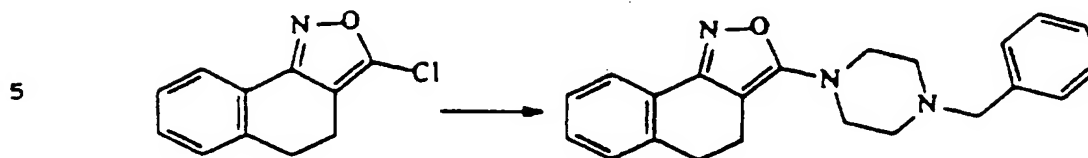
A stirred mixture of 3-chloro-4,5-dihydronaphth[1,2-c]isoxazole (5.0g, 24.4mmol), piperazine (34.2g, 397.7mmol) and  $K_2CO_3$  (6.73g, 48.7mmol) in 40ml of N-methylpyrrolidinone under  $N_2$  was lowered into an oil bath preheated to 150°C. The mixture was heated while stirring under  $N_2$  for 45 minutes. At that time, TLC ( $CH_2Cl_2$ ) showed no remaining starting material. The mixture was removed from the heating bath, allowed to cool to room temperature and extracted with  $Et_2O$ . This organic phase was washed twice with  $H_2O$ , dried over  $MgSO_4$ , filtered and concentrated in vacuo to obtain a crude solid. The solid was collected, recrystallized from heptane/ $Et_2O$  and dried in vacuo (0.1mm) at 85°C to provide pure product, mp of 97-99°C, homogeneous by TLC (silica, 1:1  $CH_3OH:CH_2Cl_2$ ,  $R_f=0.35$ ). The IR ( $CHCl_3$ ), NMR ( $CDCl_3$ ) and Mass Spectrum ( $M^+=255$ , EI, 70eV) were consistent with the structure. The yield was 3.372g (13.22mmol, 54.19%).

## Elemental Analysis

	Calculated	Found
C	70.56	70.38
H	6.71	6.67
N	16.46	16.47
O	6.27	

EXAMPLE 6

3-(4-Benzyl-1-piperazinyl) 4,5-dihydronaphth[1,2-c]isoxazole



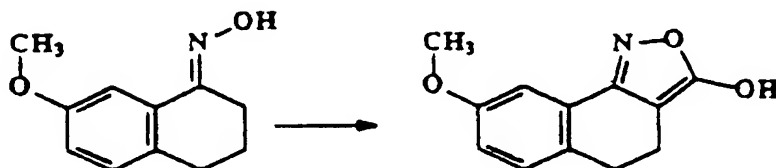
A stirred mixture of 3-chloro-4,5-dihydronaphth[1,2-c]isoxazole (2.0g, 9.75mmol), 1-benzylpiperazine (17ml, 97.5mmol) and  $K_2CO_3$  (2.7g, 19.5mmol) in 18ml of N-methylpyrrolidinone under  $N_2$  was lowered into an oil bath preheated to 150°C. The mixture was heated while stirring under  $N_2$  for 2 hours. At that time, TLC ( $CH_2Cl_2$ ) showed no remaining starting material. The mixture was removed from the heating bath, allowed to cool to room temperature and extracted with heptane. The organic phase was dried over  $MgSO_4$ , filtered and concentrated in vacuo to obtain a crude solid. The solid was collected, titrated with  $Et_2O$ , recrystallized from  $Et_2O$  and dried in vacuo (0.1mm) at 85°C to provide pure product, mp of 164-166°C, homogeneous by TLC [silica, 1:1 EtOAc,  $R_f$ =0.80]. The IR ( $CHCl_3$ ), NMR ( $CDCl_3$ ) and Mass Spectrum ( $M^+$ =345, EI, 70eV) were consistent with the structure. The yield was 1.219g (3.53mmol, 36.24%).

## Elemental Analysis

	Calculated	Found
C	76.49	76.49
H	6.71	6.85
N	12.16	12.09
O	4.63	

EXAMPLE 7

## 3-Hydroxy-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole



To a mechanically stirred mixture of 7-methoxy  $\alpha$ -tetralone oxime (5.0g, 26.18mmol) in anhydrous THF (150ml) at 0°C under N<sub>2</sub> was slowly added n-butyl-lithium (n-BuLi) (23.0ml of a 2.5M solution in hexane, 57.60mmol). The mixture was stirred at 0°C for 30 minutes, then CO<sub>2</sub> gas was bubbled into the solution. (As this addition progressed, a solid precipitate began to form). After 15 minutes, CO<sub>2</sub> addition was stopped and N<sub>2</sub> flow was restored. The thick mixture was stirred and warmed slowly to room temperature for 14 hours, then 6N H<sub>2</sub>SO<sub>4</sub> (150ml) was slowly added which dissolved the solids. The TLC showed traces of starting oxime and a mixture of desired product and an



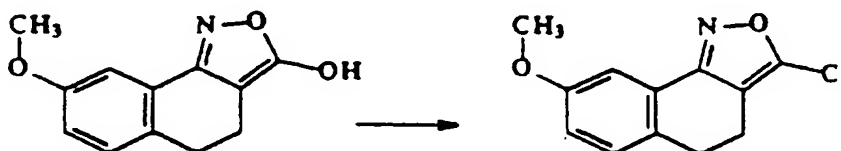
intermediate which was not isolated. Stirring was continued for 4 hours at which time the intermediate was completely converted to product. The mixture was extracted exhaustively with EtOAc. The organic fractions were combined, washed once with H<sub>2</sub>O, once with brine, dried over MgSO<sub>4</sub>, and filtered. Concentration in vacuo caused the precipitation of a solid which was collected, titrated with EtOAc, and dried in vacuo to provide the product as a solid, mp of 135-138°C, homogeneous by TLC [silica, 10:90 CH<sub>3</sub>OH:EtOAc, R<sub>f</sub>=0.46]. The IR (KBr), NMR (DMSO-d<sub>6</sub>) and Mass Spectrum (M<sup>+</sup>=217, EI, 70eV) were consistent with the structure. The yield was 2.0496g (9.45mmol, 36.08%).

## Elemental Analysis

	Calculated	Found
C	66.35	66.02
H	5.10	5.03
N	6.45	6.22
O	22.10	

## EXAMPLE 8

3-Chloro-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole



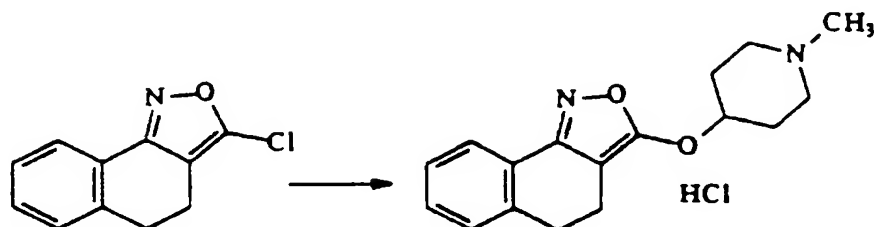
To a stirred mixture of 3-hydroxy-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole (10.0g, 46.08mmol) in phosphorus oxychloride (12.8ml, 137.3mmol), triethylamine (6.42ml, 46.08mmol) was added dropwise. After completion of addition, the mixture was heated to reflux while stirring. After 4 hours, no starting material remained as shown by TLC (silica, EtOAc). The mixture was cooled to room temperature, poured into 400ml of ice water, and extracted with heptane. The organic extracts were combined, dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. Concentration of the filtrate in vacuo caused a solid to precipitate. The solid was triturated with heptane and dried in vacuo to provide the product as needles, mp of 55-57°C, homogeneous by TLC (silica, CH<sub>2</sub>Cl<sub>2</sub>, R<sub>f</sub>=0.45). The IR (CHCl<sub>3</sub>), NMR (CDCl<sub>3</sub>) and Mass Spectrum (M<sup>+</sup>=235, EI, 70eV) were consistent with the structure. The yield was 7.75g (32.98mmol, 71.57%).

## Elemental Analysis

	Calculated	Found
C	61.16	61.29
H	4.28	4.16
Cl	15.04	
N	5.94	5.90
O	13.58	

EXAMPLE 9

3-[(1-Methyl-4-piperidinyl)oxy]-4,5-dihydronaphth[1,2-c]isoxazole



10 To a stirred solution mixture of 4-hydroxy-N-methyl  
piperidine (5.05g, 43.89mmol) in 100ml of N-methylpyrrolidinone  
under N<sub>2</sub> was added NaH (1.75g of a 60% dispersion in oil,  
43.89mmol). The mixture was stirred at room temperature for 15  
minutes, then a solution of 3-chloro-4,5-dihydronaphth[1,2-  
15 c]isoxazole (3.0g, 14.63mmol) in 15ml N-methylpyrrolidinone was  
added in one portion. The stirred mixture was lowered into an  
oil bath preheated to 150°C. After 20 minutes TLC (CH<sub>2</sub>Cl<sub>2</sub>)  
showed no starting materials remaining. The mixture was removed  
from the heating bath and allowed to cool to room temperature.  
20 It was then partitioned between heptane/H<sub>2</sub>O. The heptane phase  
was washed with water, dried over MgSO<sub>4</sub>, filtered and  
concentrated in vacuo. This crude oil obtained was taken up in  
Et<sub>2</sub>O, filtered, and the HCl salt precipitated by the addition of  
ethanolic HCl. This salt was recrystallized from CH<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O to

provide the product as a solid, mp of 147-150°C, homogeneous by  
- TLC (silica, 1:1 CH<sub>3</sub>OH:EtOAc, R<sub>f</sub>=0.02). The IR (KBr), NMR  
(CDCl<sub>3</sub>) and Mass Spectrum (M<sup>+</sup>+1=285, CI, methane) were consistent  
with the structure. The yield was 1.2994g (4.05mmol, 36.09%).

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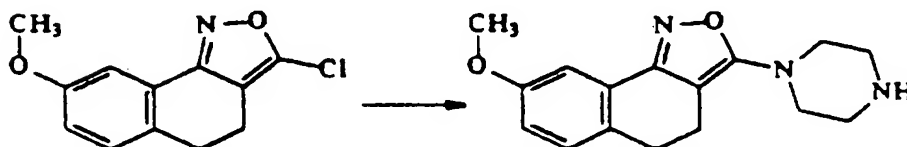
## Elemental Analysis

	Calculated	Found
C	63.65	63.55
H	6.60	6.63
Cl	11.05	
N	8.73	8.78
O	9.97	

10

## EXAMPLE 10

15 3-(1-Piperazinyl)-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole



20 A stirred mixture of 3-chloro-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole (2.0g, 8.51mmol), piperazine (7.0g, 80.6mmol) and K<sub>2</sub>CO<sub>3</sub> (2.4g, 17.1mmol) in 8.0ml of N-methylpyrrolidinone under N<sub>2</sub> was lowered into an oil bath preheated to 150°C. The mixture was heated while stirring under  
25 N<sub>2</sub> for 20 minutes. At that time TLC [CH<sub>2</sub>Cl<sub>2</sub>] showed no starting

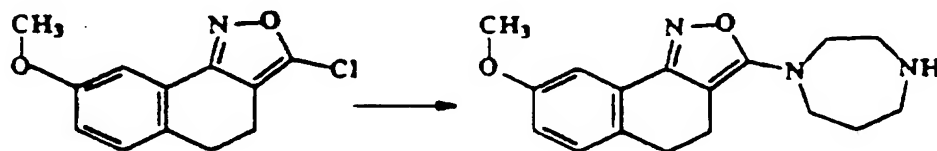
material remained. The mixture was removed from the heating bath and allowed to cool to room temperature. Upon dilution of the reaction mixture with H<sub>2</sub>O, a solid precipitated which was collected and dried in vacuo to provide pure product, mp of 86-88°C, homogeneous by TLC (silica, 1:1 CH<sub>3</sub>OH:CH<sub>2</sub>Cl<sub>2</sub>, R<sub>f</sub>=0.37). The IR (CHCl<sub>3</sub>), NMR (CDCl<sub>3</sub>) and Mass Spectrum (M<sup>+</sup>=285, EI, 70eV) were consistent with the structure. The yield was 1.932g (6.78mmol, 79.66%).

## Elemental Analysis

	Calculated	Found
C	67.35	66.99
H	6.71	6.77
N	14.73	14.53
O	11.21	

EXAMPLE 11

3-(1-Homopiperazinyl)-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole



A stirred mixture of 3-chloro-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole (2.66g, 11.32mmol), homopiperazine

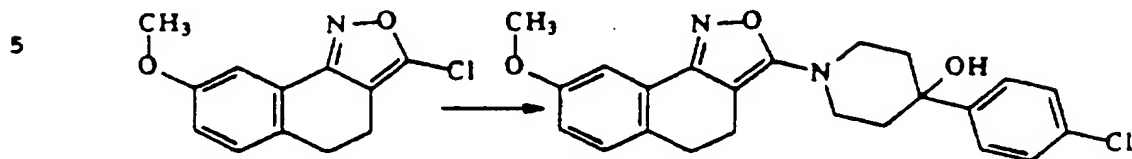
(11.40g, 113.2mmol) and  $K_2CO_3$  (3.13g, 22.68mmol) in 10.0ml of N-methylpyrrolidinone under  $N_2$  was lowered into an oil bath preheated to 150°C. The mixture was heated while stirring under  $N_2$  for 20 minutes. At that time, TLC ( $CH_2Cl_2$ ) showed no starting material remained. The mixture was removed from the heating bath, allowed to cool to room temperature and diluted with  $H_2O$ , which caused a solid to precipitate. The crude solid was dried, recrystallized from  $Et_2O$  and dried in vacuo (0.1mm) at 85°C, to provide pure product, mp of 106-109°C, homogeneous by TLC [silica, 1:1  $CH_3OH:CH_2Cl_2$ ,  $R_f=0.18$ ]. The IR ( $CHCl_3$ ), NMR ( $CDCl_3$ ) and Mass Spectrum ( $M^+=299$ , EI, 70eV) were consistent with the structure. The yield was 1.7948g (6.00mmol, 53.03%).

## Elemental Analysis

	Calculated	Found
C	68.21	68.24
H	7.07	7.11
N	14.04	14.00
O	10.69	

EXAMPLE 12

3-(1-(4-(p-Chlorophenyl)-4-hydroxy-piperidinyl)-9-methoxy-4,5-dihydronaphth[1,2-c]isoxazole



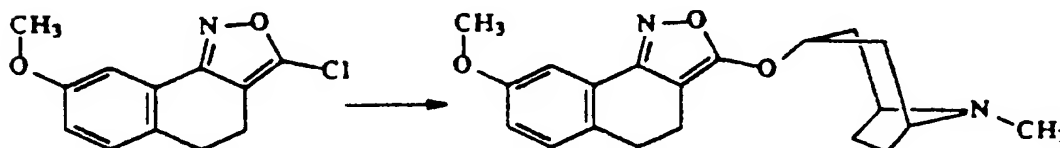
A stirred mixture of 3-chloro-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole (2.0g, 8.51mmol), 4-(p-chlorophenyl)-4-hydroxy-dipiperidine (3.6g, 17.02mol) and  $K_2CO_3$  (2.35g, 17.02mmol) in 6ml of N-methylpyrrolidinone under  $N_2$  was lowered into an oil bath preheated to 150°C. The mixture was heated while stirring under  $N_2$  for 1 hour. At that time, TLC [ $CH_2Cl_2$ ] showed no remaining starting material. The mixture was removed from the heating bath and allowed to cool to room temperature. Upon dilution of the reaction mixture with  $H_2O$ , a solid precipitated which was recrystallized from EtOAc and dried in vacuo (0.1mm) at 85°C to provide pure product, mp of 174-177°C, homogeneous by TLC [silica, 2:1 heptane:EtOAc,  $R_f=0.263$ ]. The IR ( $CHCl_3$ ), NMR ( $CDCl_3$ ) and Mass Spectrum ( $M^+=410$ , E.I., 70eV) were consistent with the structure. The yield was 2.3798g (5.60mmol, 68.20%).

## Elemental Analysis

	Calculated	Found
C	67.23	67.24
H	5.64	5.75
Cl	8.63	
N	6.82	8.78
O	11.68	

## EXAMPLE 13

10 3-[(endo)-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl]oxy]-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole



To a stirred mixture of tropine (5.41g, 38.31mmol) in 10 ml of (THF) under N<sub>2</sub> at 0°C was slowly added n-BuLi (15.0ml of a 2.5M solution in hexanes, 38.31mmol). The mixture was stirred for 15 minutes while allowed to warm to room temperature, then a solution of 3-chloro-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole (3.0g, 12.76mmol) in 30ml N-methylpyrrolidinone was added in one portion. The internal temperature increased to 99-100°C and was maintained there. After 3 hours, TLC [CH<sub>2</sub>Cl<sub>2</sub>] showed no starting material remaining. The mixture was removed from the heating bath and allowed to cool to room temperature. It was then

20

25



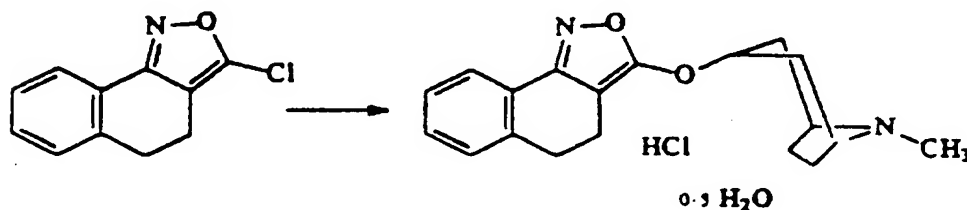
partitioned between heptane/H<sub>2</sub>O. The heptane phase was washed  
with H<sub>2</sub>O, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*,  
whereupon it solidified. This crude solid was recrystallized  
from a minimum of heptane and dried *in vacuo* to provide the  
product as a solid, mp of 102-104°C, homogeneous by TLC [silica,  
1:1 CH<sub>3</sub>OH:CH<sub>2</sub>Cl<sub>2</sub>, R<sub>f</sub>=0.20]. The IR (CHCl<sub>3</sub>), NMR (CDCl<sub>3</sub>) and Mass  
Spectrum (M<sup>+</sup>=341, CI, methane) were consistent with the  
structure. The yield was 1.3729g (4.038mmol, 31.64%).

## Elemental Analysis

	Calculated	Found
C	70.57	70.47
H	7.11	7.25
N	8.23	8.14
O	14.10	

## EXAMPLE 14

3-[(endo-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)oxy]-4,5-  
dihydronaphth[1,2-c]isoxazole hydrochloride hemihydrate



To a stirred mixture of tropine (4.4g, 31.16mmol) in 10ml

of

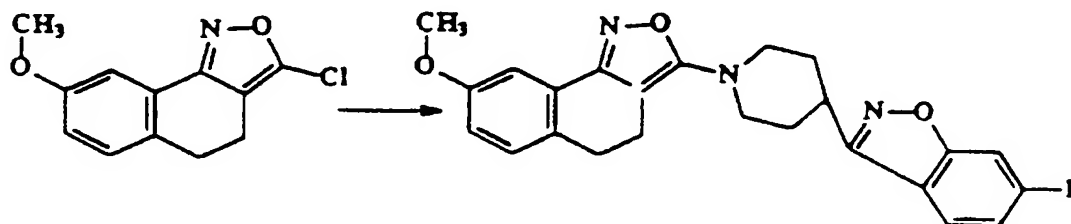
THF under N<sub>2</sub> at 0°C was slowly added n-BuLi (12.47ml of a 2.5M solution in hexanes, 31.16mmol). The mixture was stirred for 15 minutes while allowed to warm to room temperature, then a  
5 solution of 3-chloro-4,5-dihydronaphth[1,2-c]isoxazole (2.13g, 10.39mmol) in 30ml N-methylpyrrolidinone was added in one portion. The stirred mixture was lowered into an oil bath preheated to 150°C. The internal temperature increased to 85°C and was maintained there. After 3 hours, TLC (CH<sub>2</sub>Cl<sub>2</sub>) showed no  
10 remaining starting material. The mixture was removed from the heating bath and allowed to cool to room temperature. It was then partitioned between heptane/H<sub>2</sub>O. The heptane phase was washed with H<sub>2</sub>O, dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo, to provide the free base as an oil, which resisted  
15 attempts at crystallization. The oil was taken up in Et<sub>2</sub>O and the HCl salt was precipitated by the addition of ethanolic HCl. This crude solid was recrystallized from Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub> and dried in vacuo at 85°C to provide the product as a solid, mp of 167-170°C, (darkens at ca. 150°C) homogeneous by TLC (silica, 1:1  
20 CH<sub>3</sub>OH:CH<sub>2</sub>Cl<sub>2</sub>, R<sub>f</sub>=0.14]. The IR (CHCl<sub>3</sub>), NMR (CDCl<sub>3</sub>) and Mass Spectrum (M<sup>+</sup>+1=311, CI, methane) were consistent with the structure. Analysis and NMR confirmed the hemihydrate structure. The yield was 1.268g (3.563mmol, 34.29%).

## Elemental Analysis

	Calculated	Found
C	64.12	64.25
H	6.80	6.77
Cl		
N	7.87	7.70
O	9.23	

EXAMPLE 15

3-(1-(4-(6-Fluorobenzisoxazol-3-yl)-piperidiny1)-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole



A stirred mixture of 3-chloro-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole (2.0g, 8.51mmol), 4-(6-fluorobenzisoxazol-3-yl)-piperidine (2.8g, 12.76mmol) and  $K_2CO_3$  (2.35g, 17.02mmol) in 10ml of N-methylpyrrolidinone under  $N_2$  was lowered into an oil bath preheated to 150°C. The mixture was heated while stirring under  $N_2$  for 90 minutes. At that time TLC ( $CH_2Cl_2$ ) showed no remaining starting material. The mixture was removed from the heating bath and allowed to cool to room

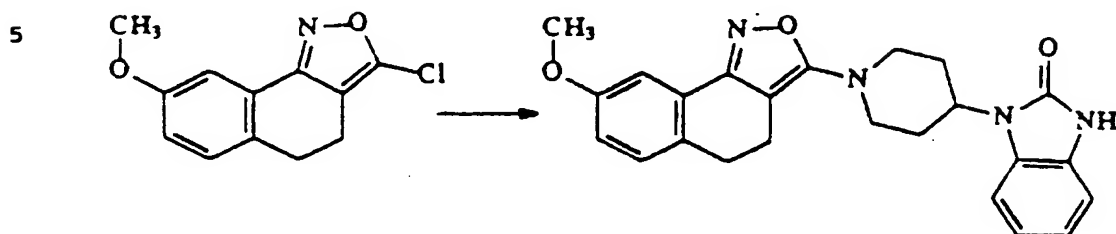
temperature. Upon dilution of the reaction mixture with H<sub>2</sub>O, a solid precipitated which was collected, dried, dissolved in CH<sub>2</sub>Cl<sub>2</sub>, and filtered through neutral alumina. The fractions containing desired product were combined and concentrated, and the resultant solid obtained was triturated with Et<sub>2</sub>O to provide a solid, mp of 181-183°C, homogeneous by TLC (silica, 2:1 Heptane:EtOAc, R<sub>f</sub>=0.15). The IR (CHCl<sub>3</sub>), NMR (CDCl<sub>3</sub>) and Mass Spectrum (M<sup>+</sup>=419, EI, 70eV) were consistent with the structure. The yield was 1.1318g (2.70mmol, 31.70%).

## Elemental Analysis

	Calculated	Found
C	68.72	68.47
H	5.29	5.28
F	4.53	
N	10.02	9.97
O	11.44	

EXAMPLE 16

3-(1-(4-2-Oxo-1-benzimidazoliny) piperidiny) -8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole



10        A stirred mixture of 3-chloro-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole (2.57g, 10.9mmol), 4-(2-oxo-1-benzimidazoliny) piperidine (4.74g, 21.8mmol) and  $K_2CO_3$  (3.02g, 21.8mmol) in 12ml of N-methylpyrrolidinone under  $N_2$  was lowered into an oil bath preheated to 150°C. The mixture was heated

15 while stirring under  $N_2$  for 4 hours. At that time, TLC ( $CH_2Cl_2$ ) showed no remaining starting material. The mixture was removed from the heating bath and allowed to cool to room temperature. Upon dilution of the reaction mixture with  $H_2O$ , a solid precipitated which was collected, dried, dissolved in  $CH_2Cl_2$ , and

20 filtered through neutral alumina using  $CH_2Cl_2$ , and then 1:1  $CH_2Cl_2$ :Et<sub>2</sub>O. The fractions containing desired product were combined and concentrated, and the resultant solid obtained was triturated with EtOAc and dried in vacuo (0.1mm Hg, 85°C) to provide a solid, mp of 211-214°C, homogeneous by TLC [silica,

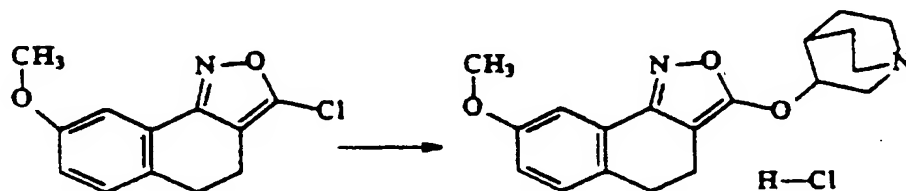
EtOAc, Rf=0.38]. The IR (CHCl<sub>3</sub>), NMR (CDCl<sub>3</sub>) and Mass Spectrum (M<sup>+</sup>=416, EI, 70eV) were consistent with the structure. The yield was 1.602g (3.85mmol, 33.33%).

#### Elemental Analysis

	Calculated	Found
C	69.21	68.88
H	5.81	5.90
N	13.45	13.10
O	11.52	

#### EXAMPLE 17

3-[(Quinuclidin-3-yl)oxy]-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole hydrochloride



To a stirred mixture of 3-quinuclidinol (4.87g, 38.28mmol) in 10ml of THF under N<sub>2</sub> at 0°C was slowly added n-BuLi (15.32g of a 2.5M solution in hexanes, 38.28mmol). The mixture was stirred for 10 minutes while allowing to warm to room temperature, then a solution of 3-chloro-8-methoxy-4,5-dihydronaphth[1,2-

c]isoxazole (3.0g, 12.76mmol) in 30ml N-methylpyrrolidinone was added in one portion. The stirred mixture was lowered into an oil bath preheated to 150°C. The internal temperature increased to 85°C and was maintained there. After 3 hours, TLC [CH<sub>2</sub>Cl<sub>2</sub>] showed no remaining starting material. The mixture was removed from the heating bath and allowed to cool to room temperature. It was then partitioned between heptane/H<sub>2</sub>O. The heptane phase was dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo to provide the free base as an oil. The oil was taken up in Et<sub>2</sub>O and the HCl salt was precipitated by the addition of ethanolic HCl. This solid was collected and dried in vacuo (0.1mm Hg, 85°C) to provide the product as a solid, mp of 133-136°C, homogeneous by TLC (silica, 1:1 CH<sub>3</sub>OH:CH<sub>2</sub>Cl<sub>2</sub>, R<sub>f</sub>=0.23]. The IR (KBr), NMR (DMSO-d<sub>6</sub>) and Mass Spectrum (M<sup>+</sup>+1=326, EI, 70eV) were consistent with the structure. The yield was 0.965g (2.39mmol, 18.79%).

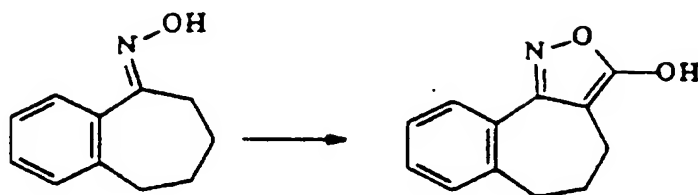
## Elemental Analysis

	Calculated	Found
C	62.89	62.91
H	6.39	6.28
Cl	9.77	
N	7.72	7.51
O	13.23	

EXAMPLE 18

5,6-Dihydro-4H-benzo[6,7]cyclohept[1,2-c]isoxazol-3-ol

5



To a mechanically-stirred mixture of 1-benzosuberone oxime (10.0g, 57.1mmol) in anhydrous THF (200ml) at 0°C under N<sub>2</sub> was slowly added n-BuLi (50.3ml of a 2.5M solution in hexane, 125.62mmol). The mixture was stirred at 0°C for 30 minutes, then CO<sub>2</sub> gas was bubbled into the solution. After 15 minutes, CO<sub>2</sub> addition was stopped and N<sub>2</sub> flow was restored. The thick mixture was stirred and warmed slowly to room temperature for 14 hours, then 6N H<sub>2</sub>SO<sub>4</sub> (220ml) was slowly added, which dissolved the solids. Stirring was continued for 18 hours, at which time the TLC [EtOAc] showed a mixture of starting oxime and product (starting oxime was best visualized using 2:1 heptane:EtOAc eluent). The mixture was poured into a separatory funnel, and the organic phase drawn off. The aqueous phase was extracted with EtOAc, and the organic phase and the EtOAc extracts were combined, washed with H<sub>2</sub>O, dried over MgSO<sub>4</sub>, and filtered. Concentration in vacuo caused the precipitation of a solid which was collected and dried in vacuo to provide the product as a



solid, mp of 165-168°C, homogeneous by TLC [silica, Et<sub>2</sub>O, R<sub>f</sub>=0.28]. The IR (KBr), NMR (DMSO-d<sub>6</sub>) and Mass Spectrum (M<sup>+</sup>=201, EI, 70 eV) were consistent with the structure. The yield was 3.0324g (15.09mmol, 26.42%).

5

## Elemental Analysis

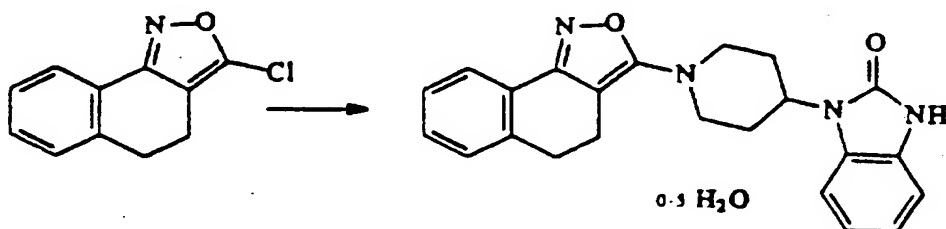
	Calculated	Found
C	71.63	71.45
H	5.51	5.50
N	6.96	6.91
O	15.90	

10

EXAMPLE 19

3-(1-(4-(2-Oxo-1-benzimidazoliny)piperidiny))-4,5-  
15 dihydronaphth[1,2-c]isoxazole hemihydrate

20



25

A stirred mixture of 3-chloro-4,5-dihydronaphth[1,2-c]isoxazole (3.1g, 15.12mmol), 4-(2-oxo-1-benzimidazoliny)piperidine (8.2g, 37.8mmol) and K<sub>2</sub>CO<sub>3</sub> (4.2g, 30.24mmol) in 18ml of N-methylpyrrolidinone under N<sub>2</sub> was lowered into an oil bath

preheated to 150°C. The mixture was heated while stirring under N<sub>2</sub> for 90 minutes. At that time, TLC (CH<sub>2</sub>Cl<sub>2</sub>) showed no remaining starting material. The mixture was removed from the heating bath and allowed to cool to room temperature. Upon  
5 dilution of the reaction mixture with H<sub>2</sub>O, a solid precipitated which was collected, dried, dissolved in CH<sub>2</sub>Cl<sub>2</sub>, and filtered through neutral alumina using CH<sub>2</sub>Cl<sub>2</sub>, and then 1:1 CH<sub>2</sub>Cl<sub>2</sub>:Et<sub>2</sub>O. The fractions containing desired product were combined and concentrated, and the solid obtained was recrystallized from  
10 EtOAc and dried in vacuo (0.1mm Hg, 110°C) to provide a solid, mp of 229-233°C, homogeneous by TLC [silica, EtOAc, R<sub>f</sub>=0.54]. The IR (KBr), NMR (CDCl<sub>3</sub>) and Mass Spectrum (M<sup>+</sup>=386, EI, 70eV) were consistent with the structure. Analysis and NMR confirmed a hemihydrate structure. The yield was 1.103g (2.79mmol,  
15 18.45%).

## Elemental Analysis

	Calculated	Found
C	69.82	70.25
H	5.86	5.64
N	14.17	14.22
O	8.28	

Preferred pharmaceutically acceptable addition salts include salts of inorganic acids such as hydrochloric, hydrobromic, sulfuric, nitric, phosphoric and perchloric acids; as well as organic acids such as tartaric, citric, acetic, succinic, maleic, fumaric, and oxalic acids.

The active compounds of the present invention may be administered orally, for example, with an inert diluent or with an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the compounds may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, waters, chewing gums and the like. These preparations should contain or form at least 0.5% of active compound, but may be varied depending upon the particular form and may conveniently be from about 4 to about 75% of the weight of the unit. The amount of compound present in such composition is such that a suitable dosage of active compound will be obtained. Preferred compositions and preparations according to the present invention are prepared so that an oral dosage unit form contains from about 1.0 to about 300mgs of active compound.

The tablets, pills, capsules, troches and the like may also contain the following ingredients: a binder such as

microcrystalline cellulose, gum tragacanth or gelatin; an  
excipient such as starch or lactose, a disintegrating agent such  
as alginic acid, Primogel™, corn starch and the like; a  
lubricant such as magnesium stearate or Sterotex®; a glidant  
5 such as colloidal silicon dioxide; and a sweetening agent such  
as sucrose or saccharin or a flavoring agent such as peppermint,  
methyl salicylate, or orange flavoring may be added. When the  
dosage unit form is a capsule, it may contain, in addition to  
materials of the above type, a liquid carrier such as fatty oil.  
10 Other dosage unit forms may contain other various materials  
which modify the physical form of the dosage unit, for example,  
as coatings. Thus tablets or pills may be coated with sugar,  
shellac, or other enteric coating agents. A syrup may contain,  
in addition to the active compounds, sucrose as a sweetening  
15 agent and certain preservatives, dyes and colorings and flavors.  
Materials used in preparing these various compositions should be  
pharmaceutically pure and non-toxic in the amounts used.

For the purpose of parenteral therapeutic administration,  
20 the active compounds of the invention may be incorporated into a  
solution or suspension. These preparations should contain at  
least 0.1% of the aforesaid compound, but may be varied from  
about 0.5 to about 30% of the weight thereof. The amount of  
compound in such composition is such that a suitable dosage of  
25 active compound will be obtained. Preferred compositions and

preparations according to the invention are prepared so that a parenteral dosage unit contains from about 0.5 to about 100mgs of active compound.

5       The solutions or suspensions may also include the following components; a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants  
10       such as ascorbic acid or sodium bisulfite; chelating agents such as EDTA; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of  
15       glass or plastic.

      The compounds of the invention may be useful as 5-HT<sub>1</sub> antagonists on the coronary chemoreflex for the treatment of anxiety, psychiatric disorders, nausea and vomiting by virtue of  
20       their ability to bind to rat entorhinal cortex membranes.

#### <sup>3</sup>H-GR 65630 Binding to Rat Entorhinal Cortex Membranes

      Studies have been performed to determine the affinity of the compounds of the invention for the 5HT<sub>1</sub> binding site in the  
25       brain. This study or assay may be useful for predicting the

potential of compounds to exhibit antiemetic, anxiolytic or atypical antipsychotic profiles.

Originally, it was believed that 5HT<sub>1</sub> binding sites existed only in the periphery. However, with the recent introduction of potent and selective 5HT<sub>1</sub> antagonist drugs such as GR65630, Zacopride, ICS 205 930 and MDL 72222 (Bemesetron,  $C_{13}H_{17}Cl_2NO_2$ ), data from binding studies have indicated that 5HT<sub>1</sub> binding sites are also located in selected areas of the brain. The highest levels of 5HT<sub>1</sub> binding sites have been detected in limbic and dopamine containing brain areas (entorhinal cortex, amygdala, nucleus accumbens and tuberculum olfactorium) (Kilpatrick, G.J. et al. Identification and distribution of 5HT<sub>1</sub> receptors in rat brain using radioligand binding. *Nature* 330: 746-748). Besides possessing selective binding in dopamine rich areas, 5HT<sub>1</sub> antagonists have been reported to block behavioral effects associated with certain drugs of abuse (nicotine and morphine) and to be active in behavioral tests predictive of anxiolytic activity. Based on these selective regional binding results and behavioral studies, 5HT<sub>1</sub> antagonists may have a therapeutic benefit in disease states believed to be associated with excessive dopaminergic activity, i.e., schizophrenia, anxiety and drug abuse.

In accordance with the above-discussed assay, a 0.05M of  
- Krebs-Hepes buffer, pH 7.4 was prepared as follows:

5                    11.92g            Hepes  
                  10.52g            NaCl  
                  0.373g            KCl  
                  0.277g            CaCl<sub>2</sub>·  
                  0.244g            MgCl<sub>2</sub>·6H<sub>2</sub>O  
10                   q.s. to 1 liter with distilled H<sub>2</sub>O,  
                  bring pH up to 7.4 (at 4°C) with 5N NaOH

                  [<sup>3</sup>H]-GR65630 (87.0Ci/mmol) was obtained from New England  
Nuclear. For IC<sub>50</sub> determinations: [<sup>3</sup>H]-GR65630 was made up to a  
concentration of 1.0nM in Krebs-Hepes buffer such that when  
15                   100μl is added to each tube, a final concentration of 0.4nM is  
                  attained in the 250μl assay.

                  GR38032F was obtained from Research Biochemical Inc.  
GR38032F was made up to a concentration of 500μM in Krebs-Hepes  
20                   buffer. 50μl of Krebs-Hepes were added to each of 3 tubes for  
                  determination of nonspecific binding (yields a final  
                  concentration of 100μM in the 250μl assay).

                  For most assays, a 50μl stock solution was prepared in a  
25                   suitable solvent and serially diluted with Krebs-Hepes buffer

such that when 50 $\mu$ l of drug is combined with the total 250 $\mu$ l assay, a final concentration from 10<sup>-5</sup> to 10<sup>-9</sup>M was attained. Characteristically, seven concentrations may be used for each assay; however, higher or lower concentrations may be used, depending on the potency of the drug.

During tissue preparation, Male Wistar rats (15-200g) were decapitated, the entorhinal cortex removed, weighed and homogenized in 10 volumes of ice cold 0.05M Krebs-Hepes buffer, pH 7.4. The homogenate is centrifuged at 48,000g for 15 minutes at 4°C. The resulting pellet was rehomogenized in fresh Krebs-Hepes buffer and recentrifuged at 48,000g for 15 minutes at 4°C. The final pellet was resuspended in the original volume of ice-cold Krebs-Hepes buffer. This yielded a final tissue concentration of 1.2 to 1.6mg/ml with the addition of 100 $\mu$ l to the assay. Specific binding was approximately 55 to 65% of the total bound ligand.

In conducting the assay, the following volumes were utilized:

100 $\mu$ l	of Tissue suspension;
100 $\mu$ l	of [ <sup>3</sup> H]-GR65630; and
50 $\mu$ l	500M GR38032F (Vehicle for binding)
	or appropriate drug concentration



Sample tubes were kept on ice for additions, then vortexed and incubated with continuous shaking for 30 minutes at 37°C. At the end of the incubation period, the incubate is diluted with 5 ml of ice-cold Krebs-Hepes buffer and immediately vacuum filtered through Whatman GF/B filters, followed by two 5ml washes with ice-cold Krebs-Hepes buffer. The filters are dried and counted in 10 ml of liquid scintillation cocktail. Specific GR 65630 binding is defined as the difference between the total binding and that bound in the presence of 100 $\mu$ M GR38032F. IC<sub>50</sub> values were derived from computer-derived log-probit analysis.

Various compounds of the invention were subjected to the above-described assay and the results the affinity for 5 HT, receptors are reported in Table I, below.

TABLE I

Affinity for 5-HT, Receptor-Displacement of <sup>3</sup>H-GR 65630

Compound	IC <sub>50</sub> , $\mu$ M
Ex. 3	0.868
Ex. 4	0.083
Ex. 5	0.056

Ondansetron (standard)	0.089
ICS 205 930 (standard)	0.039

5

Measurement of 5 HT, Antagonist Effects in the Bezold-Jarisch Assay

10 This assay evaluates the effect of these compounds as 5-HT, antagonists. They were examined in this assay on the coronary chemoreflex (Bezold-Jarisch) initiated by 5-HT, in vivo and characterized by leading inhibition of sympathetic outflow and increased activity of the cardiac vagus, leading to profound bradycardia and hypotension. The values obtained allow for  
15 continuous monitoring of arterial pressure and heart rate responses by these compounds over an extended period of time to determine their efficacy for 5 HT, antagonism.

20 The catheters were prepared from Tygon tubing (45cm length, 0.05mm, ID) bonded to Teflon tubing (0.38mm, ID). The mechanical bonding was achieved by insertion of the Teflon tubing (5mm) into the dilated (ethylene dichloride, 3-4 min.) tip of the Tygon tubing. The junction was then sealed with vinyl glue, the catheters were soaked in cold sterilization  
25 solution (Amerse instrument germicide) and flushed thoroughly

with saline prior to implantation.

Long Evans rats were anesthetized with sodium pentobarbital (50mg/kg, ip). The catheters filled with heparinized saline (100 U/ml) were inserted in the left femoral artery and vein and passed into the abdominal aorta and inferior vena cava, respectively. The catheters were then sutured to the underlying muscle and the free ends were passed subcutaneously and exteriorized through an incision on the top of the skull. The catheters were then secured to the skin with sutures, nitrofurazone powder was dusted over the area of the incision and the incision was closed using 3-0 silk sutures. The catheters were flushed with saline and sealed with metal obturators. Patency of the two catheters was maintained by daily flushing with heparinized saline (0.2 ml of 100 U/ml). The rats were given 48 hours recovery prior to obtaining cardiovascular data.

In the anesthetized rat model the catheters were not exteriorized, data was collected acutely under the influence of general anesthesia.

The baseline data Arterial Blood Pressure (mm Hg, systolic/diastolic) and Heart Rate (beats/min) were recorded and the rats were injected with 5-HT (3-7.5ug/kg, iv). The

individual response to the 5-HT intervention was determined and the compound was then administered singly or in an ascending dose range. The rats were challenged with 5-HT again at intervals postdosing and the peak response was recorded.

5

Several compounds of the invention were tested according to the above-described assay and the results are reported in Table II, below.

TABLE II

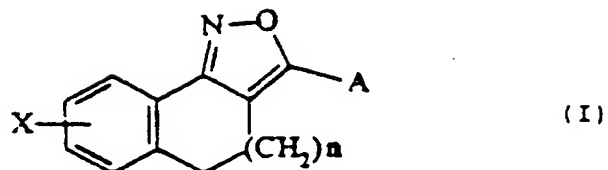
Inhibitory Potency of 5-HT<sub>2</sub> Antagonists on Reflex Bradycardia Induced by Intravenous 5-HT<sub>2</sub> in the Anesthetized Long-Evans Rat

5	Compound	Dose, mg/kg, ip	% Inhibition of Bezold-Jarisch Reflex (Values are mean $\pm$ SEM, 2-3 rats/dose)
	Ondansetron	3.0	57.3 $\pm$ 9.7
	Ondansetron	10.0	94.6 $\pm$ 2.7
	Ex. 4	0.03	58.6 $\pm$ 16.4
	Ex. 4	0.05	83.3 $\pm$ 8.2
10	Ex. 4	0.10	93.0 $\pm$ 1.0
	Ex. 5	1.0	55.6 $\pm$ 9.7
	Ex. 5	3.0	89.3 $\pm$ 2.9

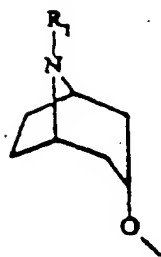
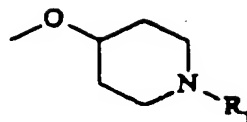
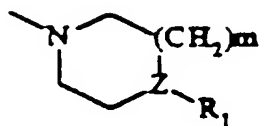
- 15 In accordance with Table II, maximal reductions in heart rate induced by 5HT<sub>2</sub> (e.g. Bezold-Jarisch reflex) occurred 15 to 60 minutes after administration.

## I Claim:

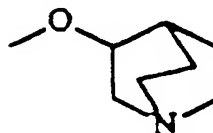
1. A compound of the formula:



where A is hydrogen, hydroxy,



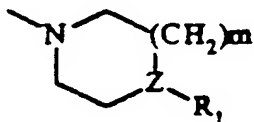
or



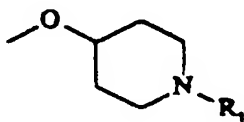
where R<sub>1</sub> is hydrogen, an alkyl group of 1 to 6 carbons, optionally substituted with hydroxy, alkoxy or amino substitution; aryl or heteroaryl, optionally substituted

with halogen, hydroxy or alkoxy; or benzyl optionally substituted with halogen, hydroxy or alkoxy;  $n$  is an integer of 1 or 2;  $Z$  is N, CH or C(OH);  $m$  is an integer of 1 to 3; and  $X$  is hydrogen, hydroxy or alkoxy; and the pharmaceutically acceptable salts thereof, and its geometric or optical isomers, or the racemic mixtures, where applicable.

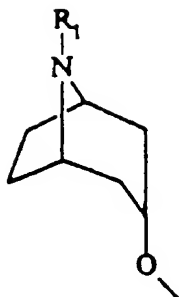
2. The compound according to Claim 1, wherein A is



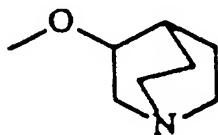
3. The compound according to Claim 1, wherein A is



4. The compound according to Claim 1, wherein A is



5. The compound according to Claim 1, wherein A is



6. The compound according to Claim 1, which is 3-chloro-4,5-dihydronaphth[1,2-c] isoxazole, its salts, isomers and racemic mixtures, where applicable.
7. The compound according to Claim 1, which is 3-hydroxy-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole, its salts, isomers and racemic mixtures, where applicable.
8. The compound according to Claim 1, which is 3-chloro-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole, its salts, isomers and racemic mixtures, where applicable.



9. The compound according to Claim 1, which is 5,6-dihydro-4H-benzo[6,7]cyclohept[1,2-c]isoxazol-3-ol, its salts, isomers and racemic mixtures, where applicable.
10. The compound according to Claim 2, which is 3-(4-methyl-1-piperazinyl)-4,5-dihydronaphth[1,2-c]isoxazole, its salts, isomers and racemic mixtures, where applicable.
11. The compound according to Claim 2, which is 3-(4-(2-hydroxyethyl)-1-piperazinyl)-4,5-dihydronaphth[1,2-c]isoxazole, its salts, isomers and racemic mixtures, where applicable.
12. The compound according to Claim 2, which is 3-(1-homopiperazinyl)-4,5-dihydronaphth[1,2-c]isoxazole, its salts, isomers and racemic mixtures, where applicable.
13. The compound according to Claim 2, which is 3-(1-piperazinyl)-4,5-dihydronaphth[1,2-c]isoxazole, its salts, isomers and racemic mixtures, where applicable.
14. The compound according to Claim 2, which is 3-(4-benzyl-1-piperazinyl)-4,5-dihydronaphth[1,2-c]isoxazole, its salts, isomers and racemic mixtures, where applicable.
15. The compound according to Claim 2, which is 3-(1-

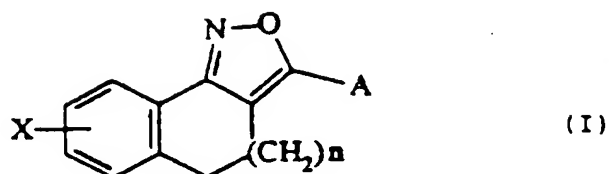
piperazinyl)-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole, its salts, isomers and racemic mixtures, where applicable.

16. The compound according to Claim 2, which is 3-(1-homopiperazinyl)-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole, its salts, isomers and racemic mixtures, where applicable.
17. The compound according to Claim 2, which is 3-(1-(4-(p-chlorophenyl)-4-hydroxy-piperidinyl)-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole, its salts, isomers and racemic mixtures, where applicable.
18. The compound according to Claim 2, which is 3-(1-(4-(6-fluorobenzisoxazol-3-yl)-piperidinyl)-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole, its salts, isomers and racemic mixtures, where applicable.
19. The compound according to Claim 2, which is 3-(1-(4-(2-oxo-1-benzimidazoliny)l)piperidinyl))-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole, its salts, isomers and racemic mixtures, where applicable.
20. The compound according to Claim 2, which is 3-(1-(4-(2-oxo-1-benzimidazoliny)l)piperidinyl))-4,5-dihydronaphth[1,2-

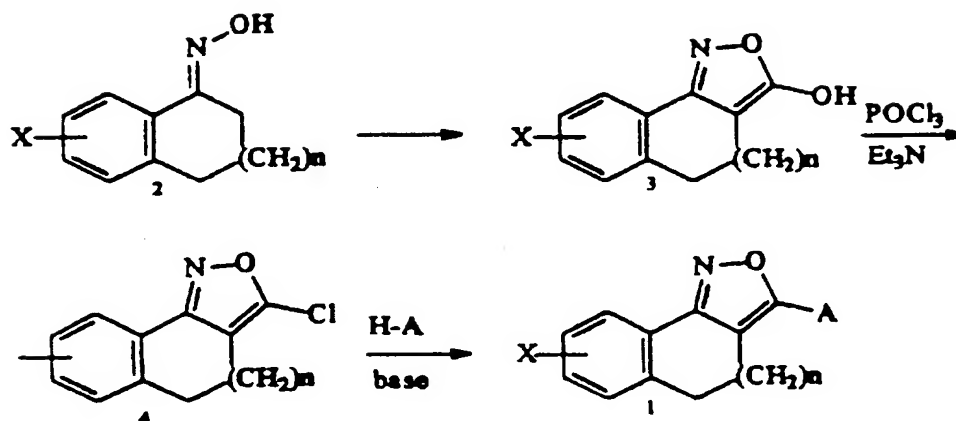
c]isoxazole hemihydrate, its salts, isomers and racemic mixtures, where applicable.

21. The compound according to Claim 3, which is 3-[(1-methyl-4-piperidinyl)oxy]-4,5-dihydronaphth[1,2-c]isoxazole, its salts, isomers and racemic mixtures, where applicable.
22. The compound according to Claim 4, which is 3-[(endo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)oxy]-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole, its salts, isomers and racemic mixtures, where applicable.
23. The compound according to Claim 4, which is 3-[(endo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)oxy]-4,5-dihydronaphth[1,2-c]isoxazole hydrochloride hemihydrate, its salts, isomers and racemic mixtures, where applicable.
24. The compound according to Claim 5, which is 3-[(quinuclidin-3-yl)oxy]-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole hydrochloride, its salts, isomers and racemic mixtures, where applicable.

25. A method of preparing a compound of the formula:



comprising the sequential reaction steps of:



26. A method of treating a patient in need of relief from a psychiatric disorder, nausea, vomiting and control of drug use, comprising providing to said patient an effective amount of the compound of Claim 1.

27. A method of treating a condition ameliorated by the use of a 5-HT<sub>3</sub> antagonist, comprising administering to a patient an effective amount to relief said condition of the compound of claim 1.
28. A pharmaceutical composition, comprising an effective amount of the compound of Claim 1, and a pharmaceutically acceptable carrier therefor.
29. A compound of Claim 1 for use as an active pharmaceutical substance.
30. The use of a compound of Claim 1 for the production of a medicament for the treatment of psychiatric disorders, nausea, vomiting and control of drug use.
31. The use of a compound of Claim 1 for the production of a medicament for the treatment of a condition ameliorated by the use of a 5-HT<sub>3</sub> antagonist.

# INTERNATIONAL SEARCH REPORT

Intern. Application No  
PCT/US 96/19569

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C07D261/20 C07D453/02 A61K31/42 C07D413/04

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ORG. PREP. PROCED. INT., vol. 23, no. 2, 1991, pages 186-188, XP000653459 M. D. SAMI ET AL.: "Synthesis and thermolysis of cycloalkenyl azides. A simple route to polycyclic isoxazoles" * Compound of formula 3a *	1
X	J. ORG. CHEM., vol. 43, no. 16, 1978, pages 3015-3021, XP000653518 G. N. BARBER, R. A. OLOFSON: "A Useful, Regiospecific Synthesis of Isoxazoles" cited in the application * Compound of formula 22 *	1

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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- \*&\* document member of the same patent family

Date of the actual completion of the international search

28 April 1997

Date of mailing of the international search report

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Name and mailing address of the ISA  
European Patent Office, P.B. 5818 Patentaan 2  
NL - 2280 HV Rijswijk  
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,  
Fax (+ 31-70) 340-3016

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Herz, C

# INTERNATIONAL SEARCH REPORT

Intern al Application No  
PCT/US 96/19569

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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Y	WO 94 10162 A (MERCK, SHARP & DOHME LTD.) 11 May 1994 see claims 1-11	1-31
Y	EP 0 402 644 A (HOECHST-ROUSSEL PHARMACEUTICALS INC.) 19 December 1990 see claims 1-15	1-31
A	DE 21 19 977 A (TEIKOKU HORMONE MANUFACTURING CO., LTD.) 16 December 1971 see page 13, line 16 - line 20; claims 1-27	1-31
A	J. MED. CHEM., vol. 19, no. 2, 1976, pages 229-239, XP000609112 M. M. HASHEM ET AL.: "Novel Pyrazolo, Isoxazolo, and Thiazolo Steroidal Systems and Model Analogs Containing Dimethoxylaryl (or Dihydroxylaryl) Groups and Derivatives. Synthesis, Spectral Properties, and Biological Activity" * Scheme VII; Compound of formula XX *	1-31
A	TETRAHEDRON, vol. 23, no. 5, 1967, pages 2081-2093, XP000612134 E. C. TAYLOR ET AL.: "Heterocyclic Syntheses from o-Aminonitriles - XXVIII. Syntheses of some benzo(f)- and benzo(h)quinazolines" * Compound of formula XXIX *	1-31

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Information on patent family members

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